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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/693,043	10/20/2000	Anders Bjorklund	17810-513 (SCI-13)	8502

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EXAMINER	
FALK, ANNE MARIE	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/693,043	BJORKLUND, ANDERS	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,13 and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed October 24, 2007 (hereinafter referred to as "the response") has been entered. No amendments have been made.

Accordingly, Claims 1-3, 6, 13, and 14 remain pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 24, 2007 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 1-3, 6, 13, and 14 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced on pages 2-4 of the Office Action mailed 8/9/06, on pages 5-8 of the Office Action mailed 11/17/05, on pages 3-5 of the Office Action mailed 2/23/05, on pages 3-7 of the Office Action mailed 6/3/04, on pages 2-9 of the Office Action mailed 5/12/03, on pages 2-5 of the Office Action mailed 7/16/02, and for further reasons as discussed herein, as containing subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for transplanting one or more deposits of about 500,000 mitogenic growth factor-responsive neural stem cells capable of differentiating into neurons, oligodendrocytes, or astrocytes to the brain, wherein the cells (a) are transplanted to a first locus of the brain of a living host subject; (b) migrate in vivo after implantation from the first locus to other anatomic sites for integration within the nervous system of the host subject following infusion of a mitogenic growth factor that does not induce differentiation of the neural stem cells at a second locus of the brain of said host subject; (c) integrate *in situ* after implantation into the parenchymal tissues at a local anatomic site in the host subject; and (d) differentiate in situ after integration into a cell selected from the group consisting of neurons, oligodendrocytes, and astrocytes, wherein the transplanted neural stem cells retain their *in vivo* responsiveness to the mitogenic growth factor. In a preferred embodiment, the neural stem cells comprise mammalian embryonic progenitor cells.

The specification fails to provide an enabling disclosure for the methods of transplantation because the specification teaches that the only use for the method is to provide a therapeutic benefit to a subject and the specification does not teach how to use the claimed methods to produce a therapeutic effect. The specification does not provide specific guidance as to how this method could be used therapeutically for any disorder. No working examples demonstrate a therapeutic effect in a diseased animal for the claimed methods. The specification contemplates that the claimed method of transplantation can be used to treat various neurodegenerative diseases and other pathological conditions (p. 16, line 29 to p. 17, line 30), such as epilepsy, stroke, ischemia, Huntington's disease, Parkinson's disease, and Alzheimer's disease (p. 16, line 30 to p. 17, line 1). The specification further contemplates use of the method of transplantation to treat demyelinating and dysmyelinating disorders, such as Pelizaeus-Merzbacher disease, multiple sclerosis, various leukodystrophies, post-traumatic

demyelination, and cerebrovascular accidents, as well as various neuritis and neuropathies, particularly of the eye (p. 17, lines 20-23). Accordingly, the specification must teach how to use the claimed method of transplantation to produce a therapeutic effect. However, the specification does not teach how to produce a therapeutic effect in any animal. The specification fails to provide specific guidance relating to the site of injection and extent of cellular persistence required to provide any therapeutic benefit for any disorder. The claims are not enabled because the transplantation of neural stem cells (NSCs), including embryonic neural stem cells, into a host has not been demonstrated to provide any therapeutic benefit to the host. The specification clearly teaches that the use for the transplant methods is to produce a therapeutic effect in the host.

The specification fails to provide an enabling disclosure for the method of cell-based therapy because methods of transplantation of neural tissue are not routinely successful and the specification does not offer adequate guidance to enable one skilled in the art to practice the claimed invention to derive a therapeutic benefit in a diseased animal. The specification teaches that the only use for the claimed method of transplantation is to produce a therapeutic effect, but the specification does not adequately teach how to use the claimed method to produce such an effect. Jackowski et al. (1995) details the limitations and unpredictability associated with the transplantation of neural tissue. At page 311, column 1, paragraph 2, the reference discusses barriers to successful transplantation of neural tissue, notably the presence of molecules that actively inhibit the regeneration of mammalian CNS and PNS axons. The specification does not teach how to overcome such problems. The specification does not offer adequate guidance as to how the claimed method could be used therapeutically for the treatment of the wide variety of disorders discussed in the specification. With regard to therapy, the specification provides general teachings only, but does not provide specific guidance for using the claimed method to treat pathological conditions. As discussed below, methods of neural stem cell transplantation are in their infancy. Therefore, considerable guidance is needed. The specification fails to provide specific guidance relating

to the site of injection and the extent of cellular persistence required and attainable in practice, to provide a therapeutic benefit for the treatment of any pathological disorder.

Milward et al. (1997) demonstrates that transplantation of neural stem cells to the CNS does not produce a therapeutic effect in a diseased animal. Milward et al. describes the transplantation of canine CNS NSCs into both rat and a shaking pup myelin mutant dog. In the rat, this resulted in the production of myelin by graft-derived cells. The authors report that the grafted cells integrated normally into the adult shaking pup cytoarchitecture. Yet despite all this, the clinical deficit of these animals was not ameliorated. Thus, it is clear that the production of myelin *in vivo* and normal integration of cells is not predictive of a therapeutic outcome. Given the unpredictability in the art of therapeutic transplantation, the development of specific therapeutic protocols requires substantial experimentation.

Mehler et al. (1999) disclose that many studies have suggested that the normal adult brain may lack the appropriate environmental signals to allow neural progenitors to realize their broad lineage potential. Specific neuropathologic conditions may alter the normal balance of regional environmental signals, for example by releasing proinflammatory and other modulatory cytokines. The presence of these inappropriate cellular cues may predispose residual neural populations to undergo apoptosis. The authors state that "[t]his suggests that it may be necessary to promote lineage commitment of progenitor cells *in vitro* prior to transplantation into a damaged brain" (p. 782, column 1, paragraph 1).

Zhang et al. (1999) report producing "robust myelination" in myelin-deficient rats upon transplantation of neural stem cells. However, despite this "robust myelination" the experiment in fact did **not** produce a therapeutic effect in the host.

Akiyama et al. (2001) describes the transplantation of clonal neural precursor cells. The cells were differentiated *in vitro* prior to transplantation. The abstract summarizes the protocol as follows:

> Neurospheres were established and the nestin-positive cells were clonally expanded in EGF and bFGF. Upon mitogen withdrawal *in vitro*, the cells differentiated into neuron- and glia-like cells as distinguished by antigenic profiles; the majority of cells in culture showed neuronal and astrocytic properties of oligodendrocytes and Schwann cells. When

> transplanted into the demyelinated adult rat spinal cord immediately upon mitogen withdrawal, the cells elicited extensive remyelination with a peripheral myelin pattern similar to Schwann cell myelination characterized by large cytoplasmic and nuclear regions, a basement membrane, and P0 immunoreactivity. The remyelinated axons conducted impulses at near normal conduction velocities.

The animal model used for the transplantation experiments was one in which a demyelinating lesion was induced. Applicant argues that the transplanted human neurospheres produced extensive remyelination and that the remyelinated axons conducted impulses at near normal conduction velocities. However, the method of Akiyama et al. is not supported in the specification, because the method taught by Akiyama et al. involved pre-differentiation of cloned cells in culture for 10 days prior to transplantation to generate a culture comprising Schwann-like cells. However, the instant specification teaches that neural stem cells are to be injected into a target area. Thus, the experiments of Akiyama et al. were not performed in accordance with the teachings of the specification. Moreover, the instant specification does not teach how to produce the Schwann-like cells that the Akiyama reference reports using in their transplantation protocol. At pages 36-37 of Akiyama et al., the authors address the question of why neural precursor cells derived from adult brain differentiate into Schwann-like cells in CNS *in vivo*. The nature of the lesion and the cellular and extracellular milieu of the transplant zone are likely to substantially influence the outcome of any given protocol. The authors note that EGF-responsive neural stem cells derived from fetal rodents formed an oligodendrocyte pattern of remyelination in myelin-deficient rats. The authors suggest that this may result from differences in fetal and adult sources of the cells or a species difference. They further suggest that the myelin-deficient rat, which has an abundance of astrocytes around the amyelinated axons, could provide a trophic influence for the differentiation of oligodendrocytes. Thus, the art teaches that the results of transplantation are unpredictable and there are no clear guidelines regarding which protocols will work or which lesions can be treated with a given protocol.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and

physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

At pages 5-11 of the response, Applicants assert that their specification and the evidence of record demonstrates that the ordinarily skilled artisan could discern an appropriate method of use without undue experimentation. Applicants point to the specification teachings relating to how to transplant CNS neural stem cells and induce migration. Applicants further assert that the graft survival and reinervation shown in the specification are indicative of a therapeutic effect. However, the art cited in this case, particularly Milward et al. demonstrate that even when grafted cells integrate normally, the clinical deficit of the animals is not ameliorated. Given the unpredictability in the art of therapeutic transplantation, the development of therapeutic protocols requires substantial experimentation. In view of the limited guidance, this substantial experimentation rises to the level of undue experimentation.

At pages 5-11 of the response, Applicant asserts that the evidence of record confirms that transplantation of neural stem cells can be routinely achieved. Applicant further asserts that such transplantation results in a therapeutic benefit to the host. No support is offered for this assertion. While non-therapeutic transplantation can be performed (i.e. cells may be implanted into the brain by a practitioner), protocols within the scope of the instantly claimed invention that produce a therapeutic effect were not available at the time of the invention, and given the state of the art, for reasons of record,

undue experimentation would have been required to develop protocols within the scope of the claims that produce a therapeutic effect in a diseased animal.

At pages 5-11 of the response, Applicant asserts that the claimed method of transplantation would be useful as a restorative therapy for neurodegenerative diseases. Applicant further asserts that the evidence of record demonstrates that the improvement of delivering a mitogenic growth factor according to the claimed methods would also provide a therapeutic benefit to the host. No support is offered for these assertions, except to point broadly to the evidence of record. However, the evidence of record has already been addressed in detail in the prior Office Actions, particularly at pages 5-9 of the Office Action of 5/12/03 and pages 6-7 of the Office Action of 6/3/04.

At page 6 of the response, Applicants assert that they do not believe that the law requires the demonstration of a therapeutic benefit. However, the only utility asserted in the specification for the claimed method is to produce a therapeutic effect. Thus, the specification must provide adequate guidance to enable one of skill in the art to achieve the asserted utility. The specification asserts no utility for non-therapeutic transplantation. Applicants cite the decision of the Board of Patent Appeals and Interferences in Appeal No. 2005-2594. However, in that case, the Board accepted that a treatment effect could be rendered by the claimed method based on the prophetic examples of the specification, which the Board understood to be actual working examples.

Applicants arguments and the evidence filed with the after final response were fully considered but were not found to be persuasive. Applicants assert that the neurospheres recited in the claimed methods are presently involved in Phase I human clinical trials for the treatment of lysosomal storage disorders. Applicants' arguments are not commensurate in scope with the claims because the claims broadly encompass the treatment of any disease or disorder by the instantly claimed transplantation method, whereas the evidence submitted is limited to treatment of neuronal ceroid lipofuscinosis. Moreover, the method to be used in the Phase I trial appears to be distinct from the instantly claimed

method, which requires infusion of a mitogenic growth factor in addition to transplantation of cells. Furthermore, the instant specification does not provide specific guidance for treating neuronal ceroid lipofuscinosis using the claimed method, nor does it describe a method for treating neuronal ceroid lipofuscinosis as set forth in Exhibit 1 now provided by Applicants, Thus, there is no evidence that the method approved by the FDA for Phase I clinical trial for treatment of neuronal ceroid lipofuscinosis was developed from the teachings of the instant specification using nothing more than routine experimentation. The exhibit provided by Applicants does not provide evidence that the protocol being studied in the Phase I clinical trial is the protocol presently claimed. There is no indication that a mitogenic growth factor is infused at a second site from where the cells are administered. Accordingly, the rejection is maintained for reasons of record.

Given the unpredictability in the art of therapeutic transplantation, the development of therapeutic protocols requires substantial experimentation. In view of the limited guidance, this substantial experimentation rises to the level of undue experimentation.

Conclusion

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing

date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk, Ph.D. whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632